Antiviral treatments
for influenza

IMMUNISATION COALITION

Incorporating the INFLUENZA SPECIALIST GROUP ISG

Vaccination remains the first line of defence against influenza, particularly in those most vulnerable to serious outcomes. However vaccination is neither universally adopted nor always protective against infection, so antiviral therapy is an important component of our capacity to treat and prevent influenza.

Specific antiviral medications active against influenza viruses have been available on prescription in Australia for over a decade, but they have not been widely used here other than during the 2009 pandemic. This may reflect lack of familiarity with their use, uncertainty about which patients have influenza, and uncertainty about which patients will derive the greatest benefit.

As with all prescription medications, the treating practitioner makes a decision about the appropriateness of antiviral therapy for their patient. The decision should take into account the likelihood that they have influenza infection (based on influenza activity, exposure risk, and their vaccination status), the severity of the acute illness, underlying medical conditions that predispose the patient to more severe influenza, the time since onset of symptoms, the economic and social impact of the illness, and the risk of spread to susceptible contacts.

This guide has been prepared by the Influenza Specialist Group to assist medical practitioners in making treatment decisions for patients presenting with influenza-like illness, particularly those most vulnerable to severe disease, and for short-term prophylaxis.

Which antiviral treatments are available in Australia?

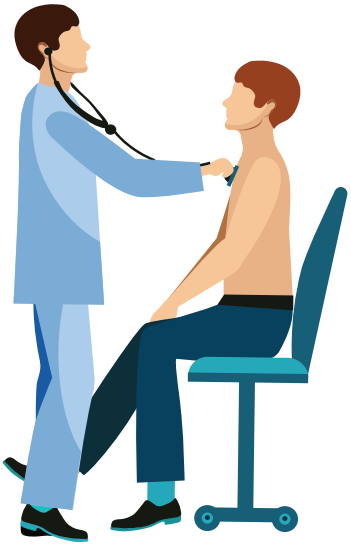
Currently there are two specific antiviral medicines active against influenza viruses registered for use in Australia. They are:

Oseltamivir, an oral capsule formulation (marketed as Tamiflu)

Zanamivir, an inhaled formulation (marketed as Relenza).

How do influenza antiviral drugs work?

Oseltamivir and zanamivir are both **neuraminidase inhibitors**. They act in a similar way by blocking the activity of the neuraminidase enzyme, which in turn stops the release of virus from infected cells and restricts further progression within the body.



WHEN TO USE NIs

The neuraminidase inhibitors (NIs) oseltamivir and zanamivir are currently the only recommended antiviral agents for the treatment or prevention of influenza in Australia.* They have been shown to limit the duration and severity of illness due to influenza if they are commenced within 48 hours of onset of illness, in both clinical trials and observational studies. The most recent meta-analysis of the oseltamivir data shows a one day reduction in the duration of symptoms, a 44% reduction of lower respiratory tract complications and a 63% reduction of hospital admissions in influenza-infected patients treated with oseltamivir.[1] Other studies have shown a reduction of otitis media in young children and of antibiotic use. The more limited data on zanamivir indicates similar benefits for treatment of uncomplicated influenza in outpatient settings. Zanamivir is not recommended for hospitalised patients or more severe influenza.

* Amantadine has been used in the past for treatment and prevention of influenza A, but it is no longer recommended for use due to high levels of resistance.

TREATMENT WITH NIs

Treatment should commence as soon as possible after the onset of illness, and should not be delayed while awaiting laboratory test results. Conventional laboratory tests usually do not provide results quickly enough to inform decisions about treatment. Point of care tests and direct immunofluorescence tests, which are reliable if positive, cannot be used to exclude influenza. New developments in the PCR-based tests may improve this situation in the future but, at present, decisions about treatment will usually need to be clinically based in order to allow treatment to commence as early as possible.

For mild/moderate illness, treatment commenced beyond 48 hours is very unlikely to be effective. However, for patients hospitalised with more severe respiratory tract infections, treatment can be commenced up to 4-5 days after onset and reduces the risk of progression of disease.[2] During the 2009 H1N1 pandemic a number of studies showed that early treatment of hospitalized patients reduced progression of disease and probably reduced mortality.

Can influenza develop antiviral resistance?

Resistance to oseltamivir is very low, but occasional strains do emerge and circulate within the community, though they are not sufficiently common to lead to a change in recommendations. Zanamivir resistance is extremely rare.

CURRENT AUSTRALIAN LICENSED INDICATIONS

Oseltamivir

- Treatment of infections due to influenza A and B viruses in adults and children aged 1 year and older. Treatment should commence as soon as possible, but no later than 48 hours after the onset of the initial symptoms of infection.
- Prevention of influenza in adults and children aged 1 year and older.

Zanamivir

- Treatment of infections due to influenza A and B viruses in adults and children aged 5 years and older. Treatment should commence as soon as possible but no later than 48 hours after the onset of the illness
- Prophylaxis of infection due to influenza A and B in adults and children (greater than or equal to 5 years) to reduce transmission among individuals in households with an infected person.
- Prophylaxis of influenza A and B during community outbreaks only in circumstances where such prophylaxis is justified (e.g. when vaccine that antigenically matches circulating influenza is not available or there is a pandemic)
- It is not recommended for routine prophylaxis against influenza infection.

SIDE EFFECTS

Side effects are uncommon and generally mild. Oseltamivir may cause nausea and vomiting. There have been post-marketing reports of rare transient neuropsychiatric events, mainly among Japanese adolescents and adults. Zanamivir may also cause gastrointestinal disturbances (diarrhoea, nausea), headache, dizziness and, because it is inhalational, it may also cause upper airways congestion, sinusitis, bronchitis and cough. Oseltamivir is the preferred drug for pregnant women.

HOW EFFECTIVE ARE NIs?

NIs can also be used to prevent influenza in contacts of infected individuals, with an effectiveness of 70% to 90% in preventing influenza and are useful adjuncts to influenza vaccination. This is most often used for control of institutional outbreaks, especially in high risk settings such as long term residential care facilities. It can also be used for prevention of illness in high risk individuals who lack vaccine-induced protection. This includes those within two weeks of vaccination, severely immunosuppressed patients, and people who have contraindications to vaccination.

The NIs are active against all known influenza virus types and subtypes, including the A/H5N1 and A/H7N9 avian influenza viruses, but not against any other respiratory viruses. Resistance to oseltamivir is very low, but occasional strains do emerge and circulate within the community, though they are not sufficiently common to lead to a change in recommendations. Zanamivir resistance is extremely rare.

ISG RECOMMENDATIONS

Antiviral treatment for seasonal influenza should be considered where the patient has clinical illness suggestive of influenza and a reasonable risk of exposure, i.e. either:

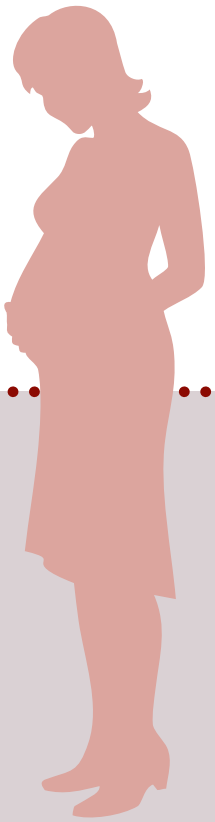
- It is during the local influenza season (remember that the influenza season in northern Australia often begins in January or February)
- They have recently travelled in areas with influenza activity
- They have had exposure to a known or likely influenza-infected person, e.g. during an institutional or travel-related outbreak.

If so, treatment with a neuraminidase inhibitor is:

- Recommended for persons with mild/moderate illness at the time of consultation but who are at higher risk of influenza complications (as defined in the US treatment guidelines[2] and Australian vaccination guidelines[3]) and who are within 48 hours of onset of illness. Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for high-risk outpatients. Prior vaccination does not preclude the use of antivirals.
- Strongly recommended for patients with severe illness that is known or suspected to be due to influenza, up to 5 days after onset of illness. This includes anyone requiring hospitalisation and anyone who has progressive, severe or complicated illness. This decision should be independent of whether they have been vaccinated against influenza or their prior state of health. Only oseltamivir is recommended in these patients.
- To be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza if treatment can be initiated within 48 hours of illness onset. This should be based on clinical judgment of the likely benefits.
- May be considered for short-term prophylaxis of close contacts, particularly in household settings and institutional influenza outbreaks.[1]

REFERENCES:

1. Dobson J et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015;
2. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed January 25th, 2016.
3. http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4



Persons at higher risk for influenza complications include:

- All adults aged 65 years and older
- All persons with a range of chronic illnesses including cardiac, respiratory, neurological, endocrine (diabetes), renal and immunological disorders
- Smokers
- Women who are pregnant
- Persons with significant obesity (BMI ≥30 kg/m^2)
- Persons aged younger than 10 years who are receiving long-term aspirin therapy
- Aboriginal and Torres Strait Islander people
- Residents of nursing homes and other long-term care facilities
- People with Down syndrome
- Homeless people
- Children aged less than 5 years.

Published by the Immunisation Coalition 2016
Suite 1222, 1 Queens Road, Melbourne, Victoria 3004
T: 03 9863 8650 E: info@immunisationcoalition.org.au

The Immunisation Coalition (IC) is a not for profit organisation, consisting of medical and scientific specialists from around Australia and New Zealand, with an expertise in immunisation and infectious diseases. The Influenza Specialist Group (ISG) is a special interest group within the Immunisation Coalition.

Follow us on Twitter: www.twitter.com/immunisationgap

Find us on Facebook: www.facebook.com/immunisationcoalition

Additional copies of this document can be downloaded from our website.

Visit **www.immunisationcoalition.org.au**, **www.isg.org.au**, **www.flusmart.org.au** and **www.pneumosmart.org.au**

IMMUNISATION COALITION

FLUSMART

ISG Influenza Specialist Group